REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this amendment, claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, 51-55, 65-68, 70-77, and 79-86 are pending. Claims 1, 6, 8, 10-17, 19-21, 31, 35, 38, 40, 42-49, 51-53, 66-68, 70-77, and 79-82 are amended. Claims 5, 7, 9, 18, 37, 39, 41, 50, 56-64, 69, and 78 are cancelled. Claims 83-86 are new. Claims 22-30 are withdrawn. The amendments do not introduce new matter or raise new issues that would require further consideration and/or search.

Applicant filed a response to a First Office Action, dated September 27, 2002, on January 23, 2003. The claim set filed in this response contained claims 1-65 ("original claim set"). On August 15, 2003, during a telephone conference with the Examiner, Applicant requested and received approval to file a Supplemental Amendment. This Supplemental Amendment, containing claims 1-82, was submitted on August 19, 2003. Copies of the materials submitted on August 19, including a cover letter, Supplemental Amendment, Transmittal Form, and USPTO Date-stamped Return Receipt Postcard, are enclosed.

Since new claims 83-86 are submitted in this Response to the Second Office Action, the "updated claim set" contains claims 1-86.

In this Second Office Action, the Examiner refers to this application as containing claims 1-65. Therefore, it appears that the rejections in the Second Office Action are in reference to the original claim set, rather than the updated claim set. Therefore, Applicant respectfully requests that the Examiner apply the traversals for claims 1-65 below to claims 66-86 in the updated claim set.

II. The Invention

The examined claims are drawn to methods for modifying glycosylation patterns of glycopeptides, including recombinantly produced glycopeptides. Also provided are glycopeptide compositions in which the glycopeptides have a uniform glycosylation pattern.

III. Support for the Amendments

Support for the amendments to the claims can be found throughout the specification and the claims as originally drafted.

Claims 1, 8, 10-17, 19-21, 31, 35, 40, 42-49, 51-53, 66-68, 70-77, and 79-82 are amended.

Claim 1 is amended in several places in this Office Action Response. First, the descriptions of the first fucosyltransferase are moved from the first paragraph of the claim into a separate fourth paragraph. This amendment is presented to correct a minor typographical error. Second, the term "is eukaryotic" is added to further describe the first fucosyltransferases in claim 1. Support for this amendment can be found in the 'Summary of the Invention' on page 12, line 10. Third, the acceptor moiety has been further defined by the term "wherein said acceptor moiety comprises a member selected from Galβ1,4GlcNAc-OR and NeuAcα2,3Galβ1,4GlcNAc-OR, wherein R is an amino acid, a saccharide, an oligosaccharide or an aglycon group having at least one carbon atom and is linked to or is part of a glycopeptide." Support for this recitation is found in originally filed claim 18.

Claims 8, 10-17, 19-21, 40, 42-49, and 51-53 are amended in order to present the claim dependencies in a uniform manner. These amendments are presented to correct minor typographical errors.

Claims 16 and 48 are amended in order to place the claims in proper Markush format. These amendments are presented to correct minor typographical errors.

Claim 31 is amended in several places in this Office Action Response. First, the descriptions of the first fucosyltransferase are moved from the first paragraph of the claim into a separate fourth paragraph. This amendment is presented to correct a minor typographical error. Second, the term "is eukaryotic" is added to further describe the first fucosyltransferases in claim 31. Support for this amendment can be found in the 'Summary of the Invention' on page 12, line 10. Third, the acceptor moiety has been further defined by the term "wherein said acceptor moiety comprises a member selected from Galβ1,4GlcNAc-OR and

NeuAcα2,3Galβ1,4GlcNAc-OR, wherein R is an amino acid, a saccharide, an oligosaccharide or an aglycon group having at least one carbon atom and is linked to or is part of a glycopeptide." Support for this recitation is found in originally filed claim 50.

Claim 35 is amended to correct a misspelling of the word 'fucosyltransferase'. This amendment is presented to correct a minor typographical error.

The term "is eukaryotic" is added to further describe the first fucosyltransferases in claims 66-68, 70-77, and 79-82. Support for this amendment can be found in the 'Summary of the Invention' on page 12, line 10.

In claims 75-77, and 79-82, the descriptions of the first fucosyltransferase are moved to consolidate their presence in one part of the claims. These amendments are presented to correct minor typographical errors.

Applicant has presented claims that are similar in scope to the claims that were examined. The amended claims are not outside of the Group originally elected. No new matter has been added by the amendments.

IV. The New Claims

Support for the new claims can be found throughout the specification and the claims as originally drafted.

New claim 83 is claim 1 rewritten in independent form without the limitation on the acceptor moiety and with a specific recitation of FucT-VI.

New claim 84 is claim 1 rewritten in independent form without the limitation on the acceptor moiety and with a specific recitation of FucT-VII.

New claim 85 is claim 31 rewritten in independent form without the limitation on the acceptor moiety and with a specific recitation of FucT-VI.

New claim 86 is claim 31 rewritten in independent form without the limitation on the acceptor moiety and with a specific recitation of FucT-VII.

V. The Responses to the Rejections

Under 35 U.S.C. § 112, First Paragraph, written description

Claims 1-21 and 31-65 of the original claim set are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Claims 5, 7, 9, 18, 37, 39, 41, 50, and 56-64 are canceled, thus mooting the rejection of those claims. The Examiner alleges that the above mentioned claims should be rejected since polypeptide sequences of the fucosyltransferases have not been disclosed in the specification. However, since the claim set discloses a method of using fucosyltransferases rather than the compositions of matter themselves, and since Applicant adequately describes these methods of using fucosyltransferases, the written description requirements for claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, and 51-55 are satisfied. Therefore, Applicant respectfully traverses the rejection.

The written description requirement is satisfied when a representative number of species of the claimed invention are described. This principle is exemplified by *In re Herschler,* 200 USPQ 711 (C.C.P.A. 1979) ("*Herschler*"); MPEP § 2163(II)(A)(3)(a)(ii). In that case, the claimed invention was the use of DMSO to enhance delivery of physiologically active steroids, and the specification provided one example demonstrating the efficacy of the claimed methods. The Patent Office rejected the claims, in part, for lack of written description for not disclosing a representative number of physiologically active steroids. The C.C.P.A. reversed the Patent Office's rejection of these claims, reasoning that, because the invention was not the discovery of novel steroidal agents but a method of delivering the agents in combination with DMSO, explicit written disclosure of all steroidal agents was not required to meet the written description requirement. Therefore, the written description requirement does not require all species of every claim term to be disclosed; rather, only an adequate description of the claimed invention.

In the present case, the claimed invention is not a fucosyltransferase. Although Applicant limits the invention in claim 1 to four kinds of fucosyltransferases, and combinations thereof, the four kinds of fucosyltransfersases are not the invention. Rather, the invention is a

novel method of using these fucosyltransferases to modify glycosylation patterns of glycopeptides. At least four illustrations of these methods of using are provided in the Examples of the specification (Example 1.2, Example 2, Example 3.2, and Example 4). As shown in *Herschler*, one example can adequately describe the claimed methods for written description purposes. Since Applicant has provided four such examples of the claimed invention, Applicant has complied with the written description requirements as described by the MPEP and *Herschler*. Therefore, a written description rejection cannot be maintained. Accordingly, withdrawal of the rejection is respectfully requested.

Under 35 U.S.C. § 103(a)

Over Seed, Paulson, and Taylor

Claims 1-21 and 31-65 of the original claim set are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Seed, *et al.*, (PCT Publication No. 96/40881) ("Seed"), Paulson, *et al.*, (PCT Publication No. 98/31826) ("Paulson"), and Taylor, *et al.*, (U.S. Patent Pub. No. 2003/0166212) ("Taylor"). Claims 5, 7, 9, 18, 37, 39, 41, 50, and 56-64 are canceled, thus mooting the rejection of those claims. The Examiner cites Seed for teaching a method of fucosylating a peptide using a recombinantly produced FucT-III fucosyltransferase. Seed teaches the use of eukaryotic fucosyltransferases, which contain a transmembrane anchoring domain in their unmodified state. The Examiner acknowledges that Seed does not teach the fucosylation of a glycopeptide or glycosylating the fucosylated glycopeptide with a glycosyl moiety other than a fucose unit. The Examiner cites Paulson for teaching methods for *in vitro* sialylation of recombinant glycoproteins. Finally, the Examiner cites Taylor as teaching a method of making a bacterial fucosyltransferase lacking membrane anchoring domains. Unlike eukaryotic fucosyltransferases, bacterial fucosyltransferases, in their unmodified form, do not contain a transmembrane anchoring domain.

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate that (1) the references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir.

1991). As explained below, there is no motivation to combine the reference teachings since a reference expressly teaches away from the Applicant's invention. The references also fail to teach Applicant's claimed element of using eukaryotic fucosyltransferases FucT-IV, FucT-V, FucT-VI, and FucT-VII which lack transmembrane anchoring domains. Finally, as the references expressly teach away from the use of Applicant's invention and do not contain all of the Applicant's claimed elements, there can be no reasonable expectation of success derived from the references. Therefore, a *prima facie* case of obviousness has not been put forth for claims 1-4, 6, 8, 10-17, 19-21, 31-36, 38, 40, 42-49, and 51-55, and Applicant respectfully traverses this rejection.

(1) There is no suggestion or motivation to modify or combine the reference teachings

The Examiner has cited Seed, Taylor, and Paulson for teaching methods of fucosylating a glycopeptide through the use of a transmembrane domain-less eukaryotic fucosyltransferase. Since the references expressly teach away from using a transmembrane domain-less eukaryotic fucosyltransferase, the suggestion or motivation to combine is not present.

The MPEP elucidates the test for this element of the *prima facie* obviousness case:

> The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and ***all teachings in the prior art must be considered*** to the extent that they are in analogous arts. ***Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art,*** considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1989)
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> MPEP § 2143.01 (emphasis added)

"Proceeding contrary to the accepted wisdom...is 'strong evidence of unobviousness.'" *Ruiz v. Foundation Anchoring Systems, Inc.*, 234 F.3d 654, 667 (Fed.Cir. 2000)(citations omitted). Therefore, the 'motivation to combine' is taken not just from the cited references, but from the

teachings of the references as a whole. When the teachings of the references conflict, the merits of each reference must be weighed in order to decide which would be most persuasive to one of skill in the art.

The final reference cited by the Examiner is Taylor, a published U.S. patent application. Although they are not yet issued, Taylor's claims are drawn to transmembrane segment-free polypeptides having α1,3-fucosyltransferase activity. Although appearing to encompass both eukaryotic and bacterial fucosyltransferases, it is important to note that all of Taylor's working examples are drawn to bacterial fucosyltransferases, which lack transmembrane domains in their natural state. Moreover, Taylor does not discuss any potential changes in enzyme activity which may arise in a eukaryotic fucosyltransferase upon removal of the transmembrane anchoring domain. Therefore, one of skill in the art would surmise from Taylor that transmembrane domain-less eukaryotic fucosyltransferases and bacterial fucosyltransferases will have similar properties.

The teachings of Taylor are **expressly taught away from** by Costa *et al.*, Stable Expression of the Golgi Form and Secretory Variants of Human Fucosyltransferase III from BHK-21 cells, *J. Biol. Chem.*, **272**: 17, 11613-11621 (1997) ("Costa"). Costa describes a series of scientific experiments on human fucosyltransferase III (FucT-III). When this protein contains its transmembrane anchoring domain, it is capable of fucosylating the substrates for Lewis a and Lewis x. In Costa, the transmembrane anchoring domain of FucT-III was removed. Upon removal, the authors reported an unexpected change in the activity of the enzyme. While the modified FucT-III was able to fucosylate Lewis a, it lost its ability to fucosylate the substrate for Lewis x or sialyl Lewis x. This finding is summarized in Costa's abstract:

> The soluble forms of fucosyltransferase III secreted by stably transfected cells may be used for *in vitro* synthesis of the Lewis a determinant on carbohydrates and glycoproteins, ***whereas Lewis x and sialyl Lewis x structures cannot be synthesized***.
>
> Costa, *J. Biol. Chem.*, **272**:17, 11613 (abstract) (1997).
> Emphasis added.

Costa, therefore, teaches that removal of the transmembrane domain can unpredictably alter the fucosyltransferase activity.

Since the teachings of Costa directly conflict with those of Taylor, the power of the two references to one of skill in the art must be compared. MPEP § 2143.01. Costa is a scientific publication that details the unexpected results of a series of real-world experiments conducted on a eukaryotic fucosyltransferase. On the other hand, Taylor is a published patent application that does not disclose the manipulation of any eukaryotic fucosyltransferases. Since Costa's findings are based on actual experimentation with eukaryotic fucosyltransferases, while Taylor's findings do not, one of skill in the art would find the teachings of Costa to be more powerful and persuasive than the teachings of Taylor.

The power of Costa's teaching away argument is not overcome by the other references cited by the Examiner, Seed and Paulson. Since Paulson does not describe fucosyltransferases, it also does not disclose the use of transmembrane domain-less eukaryotic fucosyltransferases. While Seed discusses eukaryotic fucosyltransferases, it does not mention transmembrane domains or any circumstances that would necessitate their removal. Therefore, these references do not provide a motivation to remove the transmembrane domain from a eukaryotic fucosyltransferase. Since neither the Paulson nor Seed references are germane to the discussion in earlier paragraphs concerning transmembrane domain-less eukaryotic fucosyltransferases, the power of Costa's teaching away argument remains unmitigated.

Based on the discussion above, Costa expressly teaches away from the use of a transmembrane domain-less eukaryotic fucosyltransferase to fucosylate the substrate for Lewis x or sialyl Lewis x. In spite of these warnings in the references, Applicant succeeded in producing transmembrane domain-less eukaryotic fucosyltransferases which are capable of fucosylating the substrate for Lewis x or sialyl Lewis x. Because a reference teaches away from the Applicant's invention, there is no motivation or suggestion in the references for this feature of Applicant's invention. Because the Applicant presents surprising results that refute teachings in the references, the obviousness rejection is improper and cannot be maintained.

(2) The cited references fail to teach all of the claimed elements

The cited references fail to teach Applicant's claimed element of eukaryotic fucosyltransferases FucT-IV, FucT-V, FucT-VI, and FucT-VII without transmembrane anchoring domains. Paulson does not provide this teaching since there is no discussion of fucosyltransferases in this reference. Likewise, Seed does not provide this teaching since Seed never discusses fucosyltransferases containing transmembrane domains or how or why one of skill would wish to remove them from a eukaryotic fucosyltransferase. Finally, Taylor does not teach this element because Taylor fails to disclose how to produce a transmembrane domain-less eukaryotic fucosyltransferase. Since the claims of Applicant's invention are directed to the use of eukaryotic fucosyltransferases FucT-IV, FucT-V, FucT-VI, and FucT-VII without transmembrane anchoring domains, all of the elements of Applicant's invention are not taught by the cited references. Therefore, the *prima facie* obviousness rejection cannot be maintained.

(3) The references do not provide a reasonable expectation of success

The references also fail to provide a reasonable expectation of success in performing the Applicant's invention. As mentioned earlier, the references expressly teach away from using a transmembrane domain-less eukaryotic fucosyltransferase due to unexpected changes in the enzyme's activity. Since the references teach away from this modification, the references cannot provide a reasonable expectation of success in performing the methods of Applicant's invention. Therefore, the obviousness rejection is improper and cannot be maintained.

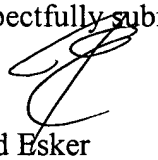
Because the references expressly teach away from Applicant's invention, the references do not contain a suggestion or motivation to modify the reference teachings. Likewise, the prior art does not teach all of the Applicant's claimed elements or provide a reasonable expectation of success. Therefore, a *prima facie* case of obviousness cannot be set forth, and Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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